(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/40073 A1

(51) International Patent Classification[7]: A61L 27/32, 27/06, 27/10, A61F 2/30, A61C 8/00

(21) International Application Number: PCT/EP00/11510

(22) International Filing Date:
20 November 2000 (20.11.2000)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/40073 A1

(54) Title: ENDOSSEOUS IMPLANT

(57) Abstract: Endosseous implant to be applied to a human or animal bone, said implant having a smooth or rough surface texture and wherein said surface has been treated with at least one organic compound carrying at least one phosphonic acid group or a salt thereof and method for producing said implant.

Endosseous Implant

The present invention relates to a metallic or ceramic endosseous implant to be applied to a human or animal bone, said implant having a smooth or rough surface texture, and wherein said surface has been treated with at least one organic compound carrying at least one phosphonic acid group [$-P(O)(OH)_2$]. Generally this phosphonic acid group is covalently bonded to the treated surface. It has been shown that such chemically modified surface surprisingly enhances the bone bonding strength. Implants according to the present invention may be used as prostheses in medicine, more specifically in orthopaedics, for replacing or strengthening broken or diseased bones, and in dentistry, for anchoring artificial teeth and for anchoring of bone anchored hearing prosthesis.

Implants which are used as prostheses in medicine for replacing or stenthening broken or diseased bones or as artificial teeth are known. These implants must be made of a non-corrosive material and must be compatible with the surrounding tissue without producing immunologic reactions effecting rejection by the body. In the following the terms "surface" or "contact surface" refer to the metallic or ceramic implant surface not yet treated according to the present invention and the term "modified surface" to the surface treated according to the present invention.

It is known that to implant devices in the form of screws, plates, nails, pins, and specially formed parts into the skeletal structure of humans and animals as artificial prosthetic is a means for permanent replacement of missing structural parts or as permanent anchoring devices. An excellent "osseointegration" is required for those situations where the implanted device should remain permanently adhered to the contacting bone surface.

The most common materials used for implants are pure and alloyed titanium, stainless steels and/or cobalt chromium alloys. When carefully produced, the titanium implant with its surface oxide exhibits biocompatibility in the sense that it remains passive

for bone regeneration and does not *per se* induce adverse reactions such as inflammation or soft tissue generation or encapsulation. The interface obtained between the implant and the bone tissue normally consists of a protein layer of about 100 nm to 1 µm thickness preventing the bone tissue from being in direct molecular contact with the implant.

The actual state of the art for endosseous implants is based on different approaches, for example (i) the creation of a suitable roughness of the implant surface giving a mechanical interlocking between bone and implant and/or (ii) coating the surface of the implant, e.g. with an artificial hydroxyapatite for improving the healing process and the bone-implant intimate contact.

It is known that a high surface roughness on titanium implants increases the mechanical stability of the implant in the bone tissue. Mechanical surface treatment significantly alters the topography, while the surface chemistry remains substantially unchanged. The disadvantages of an implant with a high surface roughness are that a purely mechanical anchoring is very sensible to micromotions which may lead to a deterioration of the mechanical anchorage and that the osseointegration time of the implant is relatively long.

Coating the surface of the implant with an artificial hydroxyapatite decreases the osseointegration time. However, it is very difficult, if not impossible, to produce hydroxyapatite coatings with a long term stability on load bearing implants. The interface between the coating and the implant is often disrupted or the coatings are flaked off.

It has now been found that if the surface of a metallic or ceramic endosseous implant has been treated with at least one organic compound carrying at least one phosphonic acid group, as described herein below, said surface shows a surprisingly improved bone bonding strength and a surprisingly shortened osseointegration time compared to the non treated surface and does not have the disadvantages as known for surfaces having a hydroxyapatite coating.

The present invention is defined in the claims. The present invention specifically refers to a metallic or ceramic endosseous implant to be applied to a human or animal bone, said implant having a smooth or rough surface texture, characterized in that said surface has been treated with at least one organic compound carrying at least one phosphonic acid group or a salt thereof.

The present invention further refers to a process for producing a metallic or ceramic endosseous implant to be applied to a human or animal bone, said implant having a smooth or rough surface texture, characterized in that said surface is treated with at least one organic compound carrying at least one phosphonic acid group or a salt thereof.

It is assumed that the phosphonate compounds as specified herein form a covalent bond with the surface of the implant thereby improving the osseointegration properties of said surface to a remarkable and unexpected extent. The present invention however is not bound to this explanation.

The metallic surface of the endosseous implant to be treated according to the present invention may be made from titanium or a titanium alloy, or any other metal or alloy which is known to be used for the production of endosseous implants, such as chromium, niobium, tantalum, vanadium, zirconium, aluminium, cobalt, stainless steels or an alloy thereof. Such metals and metal alloys for making implants are further described for example in Breme et al., Metals as biomaterials, pp. 1-71 (1998) , John Wiley & Sons Ltd, Chichester, England; J.B. Park and R.S. Lakes, Biomaterials, An Introduction (1992), 2nd Edition, Plenum Press, New York) pp. 79-115 and 293-354; R. Schmidt, Comportement des matériaux dans les milieux biologiques, Applications en médecine et biotechnologie, Vol. 7 (1999) pp. 294-343, Presses polytechniques et universitaires romandes, Lausanne, Switzerland, the contents of which are incorporated herein by reference. Most preferred are medical implants made from pure titanium or alloyed titanium.

Alternatively, the surface of the endosseous implant to be treated according to the present invention may be made from a

ceramic. Such ceramic surfaces are for example metallic surfaces which have been treated thermally or chemically or treated with a plasma or have been treated otherwise to become an oxide surface. Such treatments are known and have been described in the literature. Further the surface of the implant may have been treated thermally or chemically or treated with a plasma to become a carbide surface or nitride surface, for example a titanium surface which has been treated to become a titanium carbide or a titanium nitride surface or a titanium oxynitride or a titanium carbonitride or a titanium oxycarbide. Such treatment is known and has been described for example in H. Bender et al., Surf. Interface Anal. 14 (1989) pp. 337f, as well as in different other publications. Other ceramic surfaces which may be used within the scope of the present invention may be made for example from metal oxides, for example from aluminium oxide or zirconium oxide or silicon oxide, from apatites, preferably hydroxyapatite or fluoroapatite, or apatite like materials, preferably tri-calciumphosphate, or brushite type layers such as are described for example in Breme et al., Metals as biomaterials, pp. 219-264 (1998), ed. J.A. Helsen et al., John Wiley & Sons Ltd, Chichester, England; or J.B. Park and R.S. Lakes, Biomaterials, An Introduction (1992), 2nd Edition, Plenum Press, New York, pp. 117-140 and 169-183; or R. Schmidt, Comportement des matériaux dans les milieux biologiques, Applications en médecine et biotechnologie, Vol. 7 (1999), pp. 306-314, Presses polytechniques et universitaires romandes, Lausanne, Switzerland). Other ceramic surfaces which may be used within the scope of the present invention may be glass like surfaces made for example from silicate glass, or boron silica glass, or bioglass such as described for example in R. Schmidt, Comportement des matériaux dans les milieux biologiques. Applications en médecine et biotechnologie, Vol. 7 (1999), pp. 306-314, Presses polytechniques et universitaires romandes, Lausanne, Switzerland as well as in other literature references cited above. the contents of which are incorporated herein by reference.

Implants according to the present invention may be in the form of screws, plates, nails, pins, and specially formed parts and may

be used as prostheses in medicine, more specifically in orthopaedics, for replacing or strengthening broken or deseased bones, and in dentistry, for anchoring artificial teeth and for anchoring of bone anchored hearingprosthesis into the skeletal structure of humans and animals. The surface area of the implant which is to be bound to the body tissue resp. bones, may have a smooth or rough surface texture. Such surface textures are known and can be obtained for example by treating the surface mechanically and/or with acids and/or electrolytically and/or with a glow-discharge plasma and/or plasma spraying and/or or by electro machining. Such materials and processes have been described in different publications, for example in B.-O. Aronsson et al., J. Biomed. Mater. Res. 35 (1997), pp. 49f., the contents of which are incorporated herein by reference.

Organic compounds to be used within the scope of the present invention have at least one phosphonic acid group [$-P(O)(OH)_2$] or are a salt thereof. These compounds preferably correspond to the general formula (I):

$$A-[P(O)(OH)_2]_p \qquad (I),$$

or a salt thereof, wherein

p is a number from 1 to 6, preferably 1, 2, 3 or 4;

A is a residue of a saturated or an unsaturated hydrocarbon carrying p phosphonic acid groups, whereby said residue may be further substituted by hydroxyl and/or carboxyl; A is preferably a saturated residue of the formula $-(C_nH_{2n+2-p})-$; or

A is a residue of a protein or polypeptide of the superfamily of Transforming Growth Factor beta (TGF-ß); or a residue of a protein in the form of a Bone Morphogenic Protein (BMP) (which is a subfamily of the TGF growth factors), which stimulates the bone formation; or a residue of an amino acid; or a residue of a peptide; or a residue of a specific drug molecule, wherein each residue A carries p phosphonic acid groups.

The residue A, being a saturated or an unsaturated hydrocarbon carrying p phosphonic acid groups, may be a linear, branched or

cyclic hydrocarbon residue, which may further be interrupted by one or more oxygen and/or sulfur and/or nitrogen atoms. Suitable salts thereof are the alkali salts, preferably of sodium or potassium. Preferred is the free acid.

Examples of compounds of formula (I) wherein A is a residue of a saturated hydrocarbon [e.g. alkyl chain with 1 to 70 carbon atoms (C_1-C_{70}-Alkyl)] are monophosphonic acids such as methanephosphonic acid, ethanephosphonic acid, propanephosphonic acid or polyphosphonic acids such as methylenediphosphonic acid, propane-1,3-diphosphonic acid, ethane-1,1,2-triphosphonic acid, butane-1,1,4-triphosphonic acid, pentane-1,1,5-triphosphonic acid, pentane-2,2,5-triphosphonic acid, hexane-2,2,6-triphosphonic acid, pentane-1,1,5,5-tetraphosphonic acid, heptane-1,4,4,7-tetraphosphonic acid or propane-1,1,3,3-tetraphosphonic acid.

Examples of compounds of formula (I) wherein A is a residue of an unsaturated hydrocarbon are unsaturated monophosphonic acids and polyphosphonic acids such as those given in H. Fleisch, Bisphosphonates in bone disease, from the laboratory to the patient 2000, 4rd edition, The Parthenon Publishing Group, p.31-33, which compounds are incorporated herein by reference.

Examples of compounds of formula (I) wherein A is a residue of a protein (polypeptide) in the form of a Transforming Growth Factor beta (TGF-ß) in which are included the all members of the superfamily of growth factors and particularly the TGF-ß1, TGF-ß2, TGF-ß3, TGF-ß4, and TGF-ß5 as described for example in A.B. Roberts, M.B. Sporn, Handbook of Experimental Pharmacology, 95 (1990) pp. 419-472 or D.M. Kingsley, Genes and Development 8 (1994) p. 133-146, and references therein, where the C terminus of the peptide chain is modified with an amino-alkylphosphonic acid group, said compounds being incorporated herein by reference.

Examples of compounds of formula (I) wherein A is a residue of a Bone Morphogenic Protein (BMP) (being a subfamily to the TGF family) e.g., the BMP-2 (BMP-2a), BMP-3, BMP-4 (BMP-2b), BMP-5, BMP-6, BMP-7 (OP-1), BMP-8 (OP-2), BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, as found for example in J.M. Wozney et.al., Science 242

(1988) 1528-1534; A.J. Celeste et al., Proc. Natl. Acad. Sci. USA 87 (1990) 9843-9847; E. Özkaynak et al., J. Biol. Chem. 267 (1992) 25220-25227 ; Takao et al., Biochem. Biophys. Res. Com. 219 (1996) 656-662 ; WO 93/00432 ; WO 94/26893 ; WO 94/26892 ; WO 95/16035 and references therein, where the C terminus of the peptide chain is modified with an amino-alkylphosphonic acid group. These compounds are incorporated herein by reference.

Examples of compounds of formula (I) wherein A is a residue of an amino acid are 2-amino-4,4-bis-(diethoxy-phosphoryl)-butyric acid as described for example in O. Fabulet et al., Phosphorus, Sulfur Silicon and Related Elements, 101, 225-234 (1995); 2-amino-5-(diethoxy-phosphoryl)-pentanoic acid as described for example in I.G. Andronova et al., Russ. J. Gen. Chem. 66, 1068-1071 (1996); 2-amino-4-phosphonobutyric acid as described for example in X.Y. Jiao et al., Synth. Commun. 22, 1179-1186 (1992) and references therein. Further examples are all the principal twenty amino acids as described for example in L. Stryer, Biochemistry, 3rd edition (1988), pp. 17-22, where the amino acid is modified in an analogous way with an amino-alkylphosphonic acid group. These compounds are incorporated herein by reference.

Examples of compounds of formula (I) wherein A is a residue of a peptide are RGD-peptides, RGDS-peptides, RGDV-peptides, RGDE-peptides, and RGDT-peptides. Such peptides are described for example in Y. Hirano, J. Biomed. Materials Res., 25 (1991), pp. 1523-1534 or in WO 98/52619 and references therein. Included within the scope of the present invention are also similar peptides known to have specific biological activities such as cell attachment or cell attachment prevention, and which are prepared in analogy with the peptides as mentioned above.

Examples of compounds of formula (I) wherein A is a residue of a specific drug molecule are 1-hydroxy-3-(1-pyrrolidinyl)-propylidene diphosphonic acid, or cycloheptylamino-methylene diphosphonic acid, or 1-hydroxy-2-imidazo-(1,2-a)-pyridin-3-yl-ethylidene diphosphonic acid or 1-hydroxy-2-(3-pyridinyl)-ethylidene diphosphonic acid or (4-chlorophenyl)thio-methylene diphosphonic acid or 1-hydroxy-2-(1H-imidazole-1-yl)ethylidene diphosphonic acid

and related compounds as described for example in H. Fl isch, Bisphosphonates in bone disease, from the laboratory to the patient 2000, 4rd edition, The Parthenon Publishing Group, pp. 31-33, and references therein. Such compounds are included herein by reference.

The following steps are recommended to be taken for producing the metallic or ceramic implant according to the present invention, i.e. for treating the surface of the implant with a compound carrying at least one phosphonic acid group, preferably with the organic compound of formula (I). The implant is first cleaned in a cleaning bath for removing unwanted molecules resp. impurities from the surface. Preferably the implant is first treated with a degreasing agent, for example an organic solvent such as alcohol, chloroform, and another organic solvent and/or an inorganic detergent such as an aqueous alkaline solution based on sodium hydroxide or potassium hydroxide. Subsequently, the implant is carefully rinsed in pure water, preferably in distilled ultra-pure water, having preferably a conductivity resistance of at least 15 Mohm*cm. After cleaning and rinsing, the implant is dried with flowing nitrogen gas or flowing dry or hot air and stored under controlled conditions. Alternatively after de-greasing the implant is further treated in a glow-discharge plasma for either cleaning the surface or for producing an oxide or nitride or carbide or a combination of said surface layers, or for producing of another pre-coating layer. Such methods are described for example in B.-O. Aronsson et al. J. Biomed. Materi-als Res. 35 (1997) pp. 49-73. The clean surface of the implant is then treated with a compound carrying at least one phosphonic acid group, preferably with a compound of formula (I). The compound is brought onto the surface of the implant by any suitable means, like brushing, spraying, dipping or evaporation, including glow-discharge plasma assisted vapor deposition. The phosphonic acid compound or the salt thereof, e.g. methylene-diphosphonic acid or propane-1,3-diphosphonic acid or a sodium or potassium salt thereof, is preferably dissolved in a polar solvent, preferably in pure distilled water, so that a solution with a concentration of from about 1.0×10^{-5} mol/10 ml to 5×10^{-2}

mol/10 ml, preferably from about 5 x 10^{-4} mol/10 ml to 2.0 x 10^{-2} mol/10 ml of solvent, which preferably is distilled water. Preferably the concentration is such that a monomolecular layer is formed on the implant surface. The implant is left in contact with the surface for a few minutes up to a few hours. After that the implant is carefully rinsed with pure water and packed with a plastic or metallic clean packaging material preferably into an air tight packaging which preferably is evacuated or filled with an inert gas such as nitrogen or an inert liquid such as pure water as defined herein above. Said pure water may contain inorganic salts, preferably alkali salts, such as alkali chlorides, sulfates, phosphates, phosphonates, preferably the sodium and/or potasssium salts, and/or compounds of the formula (I) or salts thereof, preferably in a concentration of from about 1.0 x 10^{-5} mol/10 ml to 5 x 10^{-2} mol/10 ml, preferably from about 5 x 10^{-4} mol/10 ml to 2.0 x 10^{-2} mol/10 ml of solvent, which preferably is distilled water.

Analytical investigations, e.g. X-ray Photoelectron Spectroscopy analysis (XPS) or NMR, have shown that on contacting the phosphonic acid compound with the titanium surface of the implant, immediate adsorption takes place. A strong bond is formed between the surface and the phosphonic acid compound so that a chemical surface modification is obtained. Several different alkane polyphosphonic acids as mentioned herein above were synthesized. Dental implants produced with these compounds according to the present invention have shown excellent results. The following Examples illustrate but do not limit the present invention.

Example 1 (Synthesis of alkane polyphosphonic acids)

Methylenediphosphonic acid was synthesized according to US-patent 3,400,176 and B.A. Arbusov, Pure Appl. Chem. 9 (1967), pp. 307-353 and references therein. The compound was characterized by NMR (^{1}H, ^{31}P, ^{13}C), mass spectroscopic elemental analysis and by its melting point. All these data are in accordance with the literature O.T. Quimby et al., Metalated methylendiphosphonate

esters, preparation, characterization and synthetic applications, J. of Organomet. Chem. 13, 199-207 (1968).

Propane-1,1,3,3-tetraphosphonic acid was synthesized from tetraisopropyl methylenediphosphonate. The tetraphosphonic acidic solution was concentrated under vacuum, dried over P_2O_5 under vacuum. The ^1H, ^{31}P and ^{13}C NMR results (D_2O) are in accordance with the given literature data.

In an analogous manner propane-1,3-diphosphonic acid, ethane-1,1,2-triphosphonic acid, butane-1,1,4-triphosphonic acid, pentane-1,1,5-triphosphonic acid, pentane-2,2,5-triphosphonic acid, hexane-2,2,6-triphosphonic acid, pentane-1,1,5,5-tetraphosphonic acid or heptane-1,4,4,7-tetraphosphonic acid, are synthesized.

Example 2

A) A dental implant made from titanium in the form of a screw, having a diameter of 4 mm and a length of 10 mm, is produced in a conventional manner. The surface to be implanted into the body is provided with a surface roughness according to EP 0 388 575 by sandblasting the surface using an average grain size of 0.25-0.5 mm, followed by a treatment with a mixture of an aqueous acidic mixture containing a mixture of hydrochloric acid/sulfuric acid/-water in a ratio of 2:1:1, at a temperature of about 80°C for about 5 minutes so that a rough surface of the implant is obtained which is about 3.6 times larger compared to the polished surface, as measured with the voltametric method in aqueous electrolyte with 0.15M NaCl. The treated implant, resp. surface, is sonicated in bidistilled water during 15 minutes at 30°C, washed with pure water followed by sonication in water (three times) for 10 minutes and then rinsed with pure hexane and dried under vacuum (10 mm Hg, room temperature).

B) The implant as produced in chapter A) above is then put into an aqueous solution of (i) methylenediphosphonic acid [1,5 x 10^{-3} mol per 10 ml of distilled water], (ii) ethane-1,1,2-triphosphonic acid [6.2 x 10^{-4} mol/10 ml, in distilled water], (iii) pentane-1,1,5-triphosphonic acid [1.2 x 10^{-4} mol/10 ml, in distilled water], (iv) pentane-1,1,5-triphosphonic acid potassium

salt [1.2 x 10^{-4} mol/10 ml, in distilled water] and left there at room temperature for 15 minutes. The implant is then rinsed with pure water.

The implant prepared according to the preparations B(i), B(ii), B(iii) and B(iv) are implanted into the upper jaw of a mini pig. The osseointegration is measured as the torque needed to unfasten the implant from the jaw where it had osseointegrated. Comparative test results are given for the untreated implant. The results are given in Table 1. Analogous results are obtained for all the phosphonic acids given herein above. Analysis with XPS and ToF-SIMS indicated that a molecular (mono) layer was formed on a titanium surface as well as on a TiO_2-surface, and that the roughness of the surface did not seem to influence this behaviour.

Table 1

Preparation	torque* after 2 weeks (Ncm)	torque* after 3 weeks (Ncm)	torque* after 4 weeks (Ncm)
B(i)	31	72	130
B(ii)	30	80	125
B(iii)	32	79	132
B(iv)	29	83	124
Comparative Test	20	60	100

* the torque is given in Ncm as an average value from three measurements for each test.

The results illustrate the improved osseointegration of the implants according to the present invention compared to the non treated implants.

Example 3

Example 2 was repeated with the difference that the surface of the implant was chemically treated with a nitrogen plasma to yield a titanium nitride. The treatment was performed as

described in B.-O. Aronsson et al., J. Biomed. Mater. Res. 35 (1997), pp. 49f. Analogous test results were obtained as given in Table 1.

Example 4

Example 2 was repeated with the difference that the surface of the implant was treated with a methane and argon glow discharge plasma so that a surface of titanium carbide was obtained. The treatment was performed as described in B.-O. Aronsson et al., J. Biomed. Mater. Res. 35 (1997), pp. 49f. Analogous test results were obtained as given in Table 1.

Claims

1. Endosseous implant to be applied to a human or animal bone, said implant having a smooth or rough surface texture, characterized in that said surface has been treated with at least one organic compound carrying at least one phosphonic acid group or a salt thereof.

2. Implant according to claim 1, wherein the surface of the implant is made from titanium or a titanium alloy, from chromium, niobium, tantalum, vanadium, zirconium, aluminium, cobalt, stainless steel or an alloy thereof.

3. Implant according to claim 1, wherein the surface of the implant is made from a ceramic, and preferably represents an oxide surface, a carbide surface, a nitride surface, an oxynitride surface, a carbonitride surface or a oxycarbide surface.

4. Implant according to claim 3, wherein said surface is a titanium oxide or a titanium carbide or a titanium nitride or a titanium oxynitride or a titanium carbonitride or a titanium oxycarbide surface.

5. Implant according to claim 3, wherein said surface is a apatite surface, preferably made from hydroxyapatite or from fluoroapatite or from tricalciumphosphate or a brushite type surface or a silicate glass surface or a boron silica glass surface or a bioglass surface.

6. Implant according to any one of the claims 1 - 5, wherein said at least one organic compound carrying at least one phosphonic acid group corresponds to the general formula (I):

$$A-[P(O)(OH)_2]_p \qquad (I),$$

or a salt thereof, wherein

p is a number from 1 to 6, preferably 1, 2, 3 or 4;

A is a residue of a saturated or an unsaturated hydrocarbon carrying p phosphonic acid groups, whereby said residue may be further substituted by hydroxyl and/or carboxyl; preferably A is a saturated residue of the formula $-(C_nH_{2n+2-p})-$; or

A is a residue of a protein or of a polypeptide of the superfamily of Transforming Growth Factor beta (TGF-ß); or a residue of a protein in the form of a Bone Morphogenic Protein (BMP); or a residue of an amino acid; or a residue of a peptide; or a residue of a specific drug molecule, wherein each residue A carries p phosphonic acid groups.

7. Implant according to claim 6, wherein the salt of the at least one organic compound carrying at least one phosphonic acid group is an alkali salt, preferably of sodium or potassium salt.

8. Implant according to claims 6 or 7, wherein the residue A is a linear, branched or cyclic hydrocarbon residue, which optionally is further interrupted by one or more oxygen and/or sulfur and/or nitrogen atoms.

9. Implant according to any one of the claims 1 - 8, wherein the at least one organic compound is a monophosphonic acid, preferably methanephosphonic acid or ethanephosphonic acid or propanephosphonic acid; or a polyphosphonic acid, preferably selected from methylenediphosphonic acid, propane-1,3-diphosphonic acid, ethane-1,1,2-triphosphonic acid, butane-1,1,4-triphosphonic acid, pentane-1,1,5-triphosphonic acid, pentane-2,2,5-triphosphonic acid, hexane-2,2,6-triphosphonic acid, pentane-1,1,5,5-tetraphosphonic acid, heptane-1,4,4,7-tetraphosphonic acid and/or propane-1,1,3,3-tetraphosphonic acid or a salt thereof.

10. Implant according to any one of the claims 1 - 8, wherein the at least one organic compound is an unsaturated monophosphonic acid or an unsaturated polyphosphonic acid, preferably 1-hydroxy-3-(1-pyrrolidinyl)-propylidene diphosphonic acid, or cycloheptylamino-methylene diphosphonic

acid, or 1-hydroxy-2-imidazo-(1,2-a) pyridin-3-yl-ethylidene diphosphonic acid, or 1-hydroxy-2-(3-pyridinyl)-ethylidene diphosphonic acid, or (4-chlorophenyl)thio-methylene diphosphonic acid, or 1-hydroxy-2-(1H-imidazole-1-yl)ethylidene diphosphonic acid or a salt thereof.

11. Implant according to any one of the claims 1 - 8, wherein the at least one organic compound is a protein (polypeptide) in the form of a Transforming Growth Factor beta (TGF-ß) as defined by the members of the superfamily of growth factors, preferably the TGF-ß1, TGF-ß2, TGF-ß3, TGF-ß4, and TGF-ß5, wherein each time the C terminus of the peptide chain is modified with an amino-alkylphosphonic acid group or a salt thereof.

12. Implant according to any one of the claims 1 - 8, wherein the at least one organic compound is a Bone Morphogenic Protein (BMP), preferably the BMP-2 (BMP-2a), BMP-3, BMP-4 (BMP-2b), BMP-5, BMP-6, BMP-7 (OP-1), BMP-8 (OP-2), BMP-9, BMP-10, BMP-11, BMP-12, BMP-13 wherein the C terminus of the peptide chain is modified with an amino-alkylphosphonic acid group or a salt thereof.

13. Implant according to any one of the claims 1 - 8, wherein the at least one organic compound is of an amino acid or a peptide carrying at least one phosphonic acid group or a salt thereof, preferably 2-amino-4,4-bis-(diethoxy-phosphoryl)-butyric acid, 2-amino-5-(diethoxy-phosphoryl)-pentanoic acid, 2-amino-4-phosphonobutyric acid, or one of the principal twenty amino acids wherein the amino acid has been modified with an amino-alkylphosphonic acid group.

14. Implant according to any one of the claims 1 - 8, wherein the at least one organic compound is a RGD-peptide, a RGDS-peptide, a RGDV-peptide, a RGDE- peptide, and/or a RGDT-peptide which has been modified with an aminoalkylphosphonic acid group or a salt thereof.

15. Implant according to any one of the claims 1 - 8, wherein the at least one organic compound is a drug molecule carrying at least one phosphonic acid group or a salt thereof and is selected from 1-hydroxy-3-(1-pyrrolidinyl)-propylidene diphosphonic acid, cycloheptylamino-methylene diphosphonic acid, 1-hydroxy-2-imidazo-(1,2-a)-pyridin-3-yl-ethylidene diphosphonic acid, 1-hydroxy-2-(3-pyridinyl)-ethylidene diphosphonic acid, (4-chlorophenyl)thio-methylene diphos acid and/or 1-hydroxy-2-(1H-imidazole-1-yl)ethylidene diphosphonic acid.

16. Process for producing a metallic or ceramic implant according to any one of the claims 1 - 15, characterized in that said surface is treated with at least one organic compound carrying at least one phosphonic acid group or a salt thereof as defined in any one of the claims 1 - 15.

17. Implants according to any one of the claims 1 - 16 in the form of screws, plates, nails, pins, and specially formed parts and may be used as prostheses in medicine, more specifically in orthopaedics, for replacing or strengthening broken or diseased bones, and in dentistry, for anchoring artificial teeth or for anchoring of bone anchored hearing prosthesis into the skeletal structure of humans and animals.

18. Implant according to claim 17, characterized in that said implant is packed with a plastic or metallic packaging material, preferably into an air tight packaging which optionally is evacuated or filled with an inert gas or an inert liquid.

19. Implant according to claim 18, characterized in that said packaging is filled with pure water containing an inorganic salt and/or a compound of the formula (I) or a salt thereof, preferably in a concentration of from about 1.0×10^{-5} mol/10

ml to 5 x 10^{-2} mol/10 ml, preferably from about 5 x 10^{-4} mol/10 ml to 2.0 x 10^{-2} mol/10 ml of the water.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/EP 00/11510

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/32 A61L27/06 A61L27/10 A61F2/30 A61C8/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61F A61C C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, FSTA, INSPEC, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 11202 A (ICET INC) 11 March 1999 (1999-03-11) page 7, line 2 - line 15	1-10,13, 16-18
Y	page 8, line 11 - line 16 page 11, line 3 - line 20 example 1	1,11,12, 14

Y	WO 92 09697 A (CELTRIX LAB INC) 11 June 1992 (1992-06-11) page 4, line 13 -page 5, line 9 page 14, line 28 -page 15, line 8	1,11,12, 14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2001	16/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menidjel, R

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PCT/EP 00/11510

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 733 564 A (LEHTINEN RISTO TAPANI) 31 March 1998 (1998-03-31) column 1, line 20 - line 34 column 3, line 11 - line 20 column 3, line 60 -column 4, line 41 claims 1-11	1-3, 5-10, 15-19
X	US 5 646 134 A (YATES ASHLEY J) 8 July 1997 (1997-07-08) column 2, line 47 - line 67 column 4, line 14 - line 37	1,6-8, 10,15-17
X	EP 0 860 213 A (HUELS CHEMISCHE WERKE AG) 26 August 1998 (1998-08-26) page 2, line 50 - line 58 page 3, line 11 - line 55 page 6, line 20 - line 58	1-3,6,7, 10,16

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

onal Application No
PCT/EP 00/11510

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9911202 A	11-03-1999	US 6129928 A	10-10-2000
WO 9209697 A	11-06-1992	AU 651421 B	21-07-1994
		AU 9141991 A	25-06-1992
		CA 2071912 A	31-05-1992
		EP 0513334 A	19-11-1992
		US 5393739 A	28-02-1995
US 5733564 A	31-03-1998	FI 92465 B	15-08-1994
		AU 6430794 A	08-11-1994
		CA 2160565 A	27-10-1994
		CN 1120811 A	17-04-1996
		DE 69425372 D	31-08-2000
		DE 69425372 T	01-02-2001
		DE 696923 T	10-10-1996
		EP 0696923 A	21-02-1996
		WO 9423770 A	27-10-1994
		JP 8508661 T	17-09-1996
US 5646134 A	08-07-1997	AU 2374895 A	16-11-1995
		AU 3574799 A	19-08-1999
		BG 63102 B	30-04-2001
		BG 100910 A	31-03-1998
		CA 2188030 A	02-11-1995
		CN 1146152 A	26-03-1997
		CZ 9603055 A	11-06-1997
		EP 0756483 A	05-02-1997
		FI 964213 A	18-10-1996
		HR 950239 A	30-04-1997
		HU 74911 A	28-03-1997
		IL 113361 A	30-11-1999
		JP 9512268 T	09-12-1997
		NO 964441 A	18-10-1996
		PL 318552 A	23-06-1997
		SK 133396 A	07-05-1997
		TW 406021 B	21-09-2000
		US 5972913 A	26-10-1999
		WO 9528936 A	02-11-1995
		US 5891863 A	06-04-1999
		ZA 9503185 A	27-12-1995
EP 0860213 A	26-08-1998	DE 19700081 A	09-07-1998
		DE 19700082 A	09-07-1998
		DE 19700083 A	09-07-1998
		DE 19732588 A	04-02-1999
		CA 2226132 A	03-07-1998
		JP 10249277 A	22-09-1998
		NO 980018 A	06-07-1998
		US 6248811 B	19-06-2001